Antiviral therapy (cidofovir, an acyclic nucleoside phosphate) in combination with radiotherapy in HPV-positive tumours of the oropharynx: a phase 1 study.

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Primary objective ·To define the maximum tolerated dose (MTD) of cidofovir in combination with standard dose of radiotherapy in Human Papilloma Virus-positive head and neck carcinomas.Secondary Objectives·To explore p53-related gene activity in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON33865

Source
ToetsingOnline

Brief title
Antrhox

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
head and neck carcinoma - HPV-positive oropharyngeal carcinoma in the expansion cohort.

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht
Source(s) of monetary or material Support: Grant-aanvraag;industrie;stichting wetenschappelijk onderzoek KNO,Pfizer

Intervention

Keyword: cidofovir, HPV, oropharyngeal carcinoma, radiotherapy

Outcome measures

Primary outcome

Primary objective

·To define the maximum tolerated dose (MTD) of cidofovir in combination with

standard dose of radiotherapy in Human Papilloma Virus-positive head and neck

carcinomas.

Secondary outcome

Secondary Objectives

·To explore p53-related gene activity in patients before and during treatment

with Cidofovir.

·To evaluate PET/CT findings oropharyngeal carcinomas before and after

cidofovir administration.

Study description

Background summary

1.1 Background Disease Information
Head and neck squamous cell carcinoma (HNSCC) represent about 6,5% of all new cases of cancer. Abuse of tobacco and alcohol are well-established risk factors for development of HNSCC. Despite new diagnostic tools and therapies, survival rates remain low. Therefore it is important to identify new molecular markers for improvement of therapeutic strategies for HNSCC. Human Papilloma Virus

(HPV) is associated with oropharyngeal carcinoma and with increasing incidence in particular with tonsillar carcinoma (1). As the DNA of HPV integrates in the human cellular genome, oncoproteins E6 and E7 are upregulated and disable tumor suppressor genes p53 and pRb, which is a crucial step in carcinogenesis (2, 3). Depending on tumor location and HPV-type, numbers of HPV-positive HNSCC are varying (2-76%). The DNA type HPV-16 is found in 21 % of the HNSCC (50% of oropharyngeal carcinomas) (3).
The standard treatment of oropharyngeal carcinomas in the Netherlands is dependent on tumor location and TNM stage (UICC). Locoregional radiotherapy is mostly indicated in T1 and T2 oropharynx carcinoma. In T3 and T4, the treatment is surgery eventually followed by postoperative radiotherapy. In inoperable (functional) T3-T4 tumors and if surgery is refused a combined chemo radiation therapy is performed (cisplatinum).
Currently, promising results concerning the efficacy of antiviral agents for treatment in patients with HPV-positive (HPV-16 and -18) cervical carcinomas are found (4). Therefore it is proposed that antiviral therapeutic strategies in addition to radiation therapy might improve tumor response and outcome radiation in HPV-positive HNSCC.
In vitro research shows that acyclic nucleoside phosphates, like cidofovir (HPMPC) and adefovir (PMEA), inhibit tumor cell differentiation and angiogenesis (adefovir) and induce apoptosis (cidofovir) (5). In vivo, adefovir acts against choriocarcinoma in rats and cidofovir in hemangioma in rats. Cidofovir is already widely accepted in locoregional therapies for papillomatosis in humans.
Phase 1 trials regarding cidofovir in humans already have been performed for cytomegalovirus retinitis in patients with AIDS (6) with a dose of 5mg/kg intravenously every 2 weeks. A following phase 2-3 analysis administered 5mg/kg of body weight once weekly for two weeks, followed by 3 mg/kg of body weight (low-dose) and 5mg/kg of body weight (high-dose) once every two weeks (7, 8). Snoeck et al. (9) showed that local therapy with cidofovir gel 1% in cervix carcinomas (stage CIN III) results in partial or complete regression of cervical dysplasia. Tristram et al. (10) studied the effect of cidofovir in high-grade non-cervical anogenital intraepithelial neoplasias. A complete regression after local treatment with cidofovir was found. The research of Sirianni et al. (11) showed that HPV-positive cells in vitro could be radiosensitized by adding cidofovir to the radiotherapy. This was also shown in vivo as well as in nude mouse xenografts by Abdulkarim et al. (12).
We hypothesize that combining cidofovir with radiotherapy will improve the efficacy of radiotherapy in HPV-positive head and neck cancer. Therefore we propose a phase 1 trial to investigate the maximum tolerated dose of cidofovir to be combined with radiotherapy during a six-week period.

1.2 Background Therapeutic Information
Cidofovir, (S)-1-(3-Hydroxy-2-phosphonyl-methoxypropyl) cytosine, is characterised by a stable phosphonate linkage between the acyclic nucleoside and the phosphate moiety.
In a phase I/II clinical trial with intravenous cidofovir in patients with

human immunodeficiency virus (HIV) infection and asymptomatic CMV infection, prolonged and dose-dependent antiviral effects were observed at doses of 3,0 and 10,0 mg/kg of bodyweight (7, 8). The dose-limiting toxicity was nephrotoxicity, which was dose dependent and less frequent with concomitant oral probenecid and hydration. This toxicity was characterized by proximal tubular dysfunction and was consistent with observations in animal toxicity studies (7, 8). Pharmacokinetic parameters for cidofovir in these patients were dose-dependent; the mean total clearance of cidofovir from serum was approximately 150 ml/h/kg at both dose levels. This value was significant higher than the baseline creatinine clearance determined in the same patients, suggesting that active tubular secretion contributed to the renal clearance of cidofovir. There was evidence in two patients of a prolonged phase in the elimination of cidofovir. However, in the majority of patients the drug displayed a terminal elimination half-life of 3 to 4h. There were no significant changes in the pharmacokinetics of cidofovir over four infusions, suggesting that the drug did not accumulate.
The pharmacokinetics of cidofovir were examined at five dose levels in three phase I/II studies in a total of 42 HIV-infected patients (13). Levels of cidofovir in serum following intravenous infusion were dose proportional over the dose range of 1,0 to 10,0 mg/kg of body weight and declined biexponentially with an overall mean +/- standard deviation terminal half-life of 2,6 +/- 1,2h (n=25). Approximately 90% of the intravenous dose was recovered unchanged in the urine in 24h. The overall mean +/- standard deviation total clearance of the drug from serum (148 +/- 25 ml//h/kg; n=25) approximated renal clearance (129 +/- 42 ml/h/kg; n=25), which is significant higher than the baseline creatinine clearance in the same patients (83 +/- 21ml/h/kg; n=12). Active tubular secretion plays a significant role in the clearance of cidofovir. The steady state volume of distribution of cidofovir was approximately 500 ml/kg, suggesting that the drug was being distributed in total body water. Repeated dosing with cidofovir at 3,0 and 10,0 mg/kg/week did not alter the pharmacokinetics of the drug. Concomitant administration of intravenous cidofovir and oral probenecid to hydrated patients had no significant effect on the pharmacokinetics of cidofovir at a 3,0 mg/kg dose. At high doses of cidofovir, probenecid appeared to block tubular secretion of cidofovir and reduce its renal clearance to a level approaching glomular filtration.
The pharmacokinetics of cidofovir administered with probenecid were evaluated in 12 HIV-infected patients with or without asymptomatic CMV infection and 10 patients with relapsing CMV retinitis. Dose-independent pharmacokinetics were observed for cidofovir, administered with probenecid, after one hr infusions of 3.0 (n = 12), 5.0 (n = 6), and 7.5 (n = 4) mg/kg. Approximately 70 to 85% of the cidofovir dose administered with concomitant probenecid was excreted as unchanged drug within 24 hr. When cidofovir was administered with probenecid, the renal clearance of cidofovir was reduced to a level consistent with creatinine clearance, suggesting that probenecid blocks active renal tubular secretion of cidofovir.
1.3 Hypothesis
We hypothesize that combining cidofovir with radiotherapy will improve the

efficacy of radiotherapy in HPVpositive head and neck cancer. Therefore we propose a phase 1 trial to investigate the maximum tolerated dose of cidofovir to be combined with radiotherapy and/or surgery during a six-week period.

Study objective

Primary objective
·To define the maximum tolerated dose (MTD) of cidofovir in combination with standard dose of radiotherapy in Human Papilloma Virus-positive head and neck carcinomas.
Secondary Objectives
·To explore p53-related gene activity in patients before and during treatment with Cidofovir.
·To evaluate PET/CT findings oropharyngeal carcinomas before and after cidofovir administration.
End-points
·Incidence of locale and severe complications
·Grade IV or V: dermatology/skin
·Grade IV or V: musculoskeletal/soft tissue
·Grade III: renal/genitourinary
·Incidence of other acute toxicity, assessed according to CTC version 3.0

Study design

Phase 1 trial
Eligible patients will be registered in the trial and treated with a combination of radiotherapy and escalating dose of cidofovir according to the in this section described dose escalation scheme.
A biopsy of the HNSCC is taken at most two weeks prior to the combined treatment. This biopsy will be analyzed for HPV-status and p53-related gene activity. Ninety-six hours after the first dose of each dose level in each patient a second biopsy is taken in case of a first HPV-positive sample. Both samples are analyzed for p53-related gene activity. Improvement of p53-activity is expected in at least 90% of the HPV-positive HNSCC.
Changes in p53-related gene activity (Δgene exp) will be correlated with imaging of tumor at each dose level in patients with histological confirmed HPV-positive HNSCC (See also Chapter 8).
A PET-CT scan is routinely performed prior to treatment and three months after the last dose of radiotherapy. An explorative description analysis will be performed.
Patients will be followed up until four weeks after the combined treatment. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix A) at any time of presence during and follow-up after treatment when reported by patients or encountered during therapy.
After the defined period of the trial, patients will be routinely controlled at

the ENT- and radiation oncology department.

Dose Escalation Schedule for Cidofovir
The dose of cidofovir will be escalated in fixed increments according to the dose escalation scheme outlined below.

Dose Dose of cidofovir given intravenously, once a week combined with RT starting one week prior to RT (6 doses)
level Minimum number of patients
-2 1,50 mg/kg of body weight --
-1 2,50 mg/ kg of body weight --
1(SD) 4 mg/ kg of body weight 3
2 7 mg/ kg of body weight 3

Starting Dose (SD) of Cidofovir
Dose level: dose of cidofovir given intravenously, once a week during radiotherapy starting one week prior to radiotherapy (6 doses).
The starting dose of cidofovir will be 4 mg/kg of body weight weekly during radiotherapy. This dose is based on previously performed pharmacokinetic, phase 1, 2 and 3 trials. The rational for this starting dose is the recommended dose given in previous studies minus 1.

Cidofovir will be solved in 100ml NaCL 0,9% and administrated during one hour. Prior to and after administration of cidofovir the patient will receive one litre of NaCl 0,9% during one hour.
Three hours prior to cidofovir the patient will take 2 grams of probenicid orally and again 1gram 3 and 8 hours after administration of cidofovir.

Radiotherapy
Standard treatment of radiotherapy (3D conformal radiotherapy or MIRT) is applied according to clinical guidelines defined by Maastricht Radiation Oncology Clinic (appendix C).

Methods and Endpoints
Dose limited toxicity (DLT)
The rate of subject entry and escalation to the next dose level will depend upon assessment of the safety profile of patients entered at the previous dose level. Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (see Appendix A).

3+3 design
A minimum of three patients will be entered on each dose level. All three will be followed for one completed cycle of therapy (one dose/ week during 6 week) and subsequent enrolment of new cohorts will be based on the toxicity assessment in that first cycle and the documentation of any dose limiting toxicities.

Defining Maximum Administered Dose (MAD)
·If 0/3 patients exhibit dose limiting toxicity at this dose level
Dose escalation to the next dose level may begin in a new cohort of patients 4 weeks after the last radiation.

·If 1/3 patients exhibit dose limiting toxicity at this dose level:
Expand dose level to a total of 6 patients.
If no further DLT events seen, dose escalation to the next dose level may begin in a new cohort of patients.
If 1 or more further DLT events are seen (i.e. 2 or more of 6 patients), this dose level will be considered the maximum administered dose (MAD).

·If 2/3 patients exhibit dose limiting toxicity:
This dose level will be considered the maximum administered dose (MAD).

·Before opening the next higher dose level all toxic effects at the preceding dose level will be reviewed and expansion or escalation will be undertaken as appropriate.

Dose Limiting Toxicity (DLT)
·Toxicity will be graded using CTCAE version 3.0 (see Appendix A). Any dose limiting toxicity must be a toxicity that is considered related to study drug. Dose limiting toxicity is defined by disorder of at least one of the following criteria:

Hematological
1 Absolute granulocyte count (AGC) < 0.5 x 109/L
2 Febrile Neutropenia (ANC < 1.0 x 109/L, fever > 38.5oC)
3 Platelets < 25 x 109/L
4 Bleeding felt to be due to thrombocytopenia
5 Total WBC <1,0 x 109/L

Non-Hematological:
1 Diarrhea > Grade 3 despite optimal loperamide use
2 Rash > Grade 3 or grade 2 is medically concerning or unacceptable to the patient
3 Mucositis, burns > Grade 4
4 Kidney > Grade 3 despite optimal hydration and probenecid use
5 Mucosa > Grade 4
6 Bone > Grade 4
7 Other grade 3 effects thought to be treatment related.
8 Missing > 2 doses of treatment for toxicity reasons.

Recommended Phase II Dose (RP2D)
·As described above, the MTD is that dose in which 2/3 or 2/6 patients experience dose-limiting toxicity.
·The RP2D is the MTD dose level *-1*. If the MTD is seen at the starting dose

level, then dose level *-1* will be the recommended dose.
·At least 6 patients will be treated at the recommended dose to assure information on the safety profile at that dose is complete.
·To assure information on the safety profile at the RP2D in HPV-positive oropharyngeal carcinoma is complete, the RP2D will be given to an additional 6 patients with histological proven HPV-positive oropharyngeal carcinoma.
·If less then two DLT*s are observed in this cohort, the trial will be ended.

Patient Replacement
·Three patients within a dose level must be observed until 4 weeks after the last dose of radiotherapy, before accrual to the next higher dose level may begin.
·If a patient is withdrawn from the study for reasons other than DLT, an additional patient may be added to that dose level. Patients one or more doses due to toxicity will not be replaced since these patients will be considered to have experienced DLT.
·Patients may also discontinue protocol therapy in the following instances:
Intercurrent illness which would in the judgment of the investigator affect patient safety, the ability to deliver treatment or the primary study endpoints
Request by patient

Study burden and risks

One week before and during the five weeks of radiotherapy, patients are treated once weekly with intravenous cidofovir (6-administrations). One administration takesthree hours and includes observation and infusion of 1 liter of saline during one hour, infusion of cidofovir in a 100ml saline solution during one hour, and again infusion of 1 liter of saline during one hour. Before starting the weekly infusion a bloodsample is taken to control haematological parameters. This is also conducted before entering the trial and after finishing the trial (see study design). The first biopsy and the PET/CTscan are standardly performed according the ongoing guidelines. the second biopsy is optional and will be taken after agrement of the patient in case of a first HPV-positive sample, 9 hours (+/-24 hours) under local anaesthesia. Further treatment and diagnosing is performed according ongoing national guidelines.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

·UICC TNM I-IV, for which curable (high dosing) radiotherapy is advised.
·Histological proven HPV-positive oropharyngeal carcinoma in the dose escaltion schedule.
·WHO performance status 0-4
·Less then 10% weight loss the last 6 months
·Normal serum bilirubin
·Normal white blood cells, neutrophils, platelets, hemoglobin
·No prior history of head or neck radiotherapy
·No uncontrolled infectious disease
·Willing and able to comply with the study prescriptions
·Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Exclusion criteria

·Patients receiving agents with nephrotoxic potential. Such agents must be discontinued at least seven days prior to starting therapy with cidofovir.
·Hypersensitivity to cidofovir
·History of clinically severe hypersensitivity to probenecid or other sulfa-containing medications.

·History of kidney function disorder.
·Serum creatinine concentration >132,6 micromol/L, a calculated creatinine clearance /= 100mg/dL (equivalent to >/= 2+ proteinuria).
·Recent (< 3 months) severe cardiac disease (arrhythmia, congestive heart failure, infarction)
·Pregnant women.
·Age under 18 years.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2008
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Vistide
Generic name:	Cidofovir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-01-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27994
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2007-004873-25-NL
CCMO	NL19517.068.07
OMON	NL-OMON27994